April 14, 1999

**Nycomed Amersham**

**Nycomed Amersham Imaging**

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Dockets Management Branch [HFA-305]
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

**Re: FDA Docket No. 98D-0785; Draft Guidance for Industry on Developing Medical Imaging Drugs and Biologics**

Dear Sir or Madam:

These comments on the Food and Drug Administration's October 1998 "Draft Guidance for Industry: Developing Medical Imaging Drugs and Biologics" ("Draft Guidance") are submitted on behalf of Nycomed Amersham. Nycomed Amersham commends the FDA for its efforts to establish a guidance for medical imaging drugs and appreciates the opportunity to comment on the draft document. Nycomed Amersham offers the following comments.

General Comments

In many respects, the draft guidance's approach to safety and efficacy demonstrations for medical imaging drugs is very similar to FDA's approach to the establishment of safety and efficacy for therapeutic drugs. It must be emphasized that many of the properties of medical imaging drugs are distinctly different from those of therapeutic drugs. The clinical usefulness of a medical imaging drug is not directly related to its *in vivo* effects. The manner in which physicians use these products and the product's benefits to patients are also very different from the way physicians use and patients benefit from therapeutic drugs.

Medical imaging products are typically administered in small mass doses for single or limited use. They are generally rapidly and nearly completely eliminated from the body. Nycomed Amersham believes that it is inappropriate to apply the same or similar measures of safety and efficacy as those applied to therapeutic drugs.

Nycomed Amersham believes that the safety factor of 1,000 times the maximal human dose, the requisite safety factor for attaining Group 1 status, would effectively mean that no medical imaging drug would qualify for Group 1 status. Many currently approved medical imaging products, well established as very safe, would be likely to produce observable effects at such extreme doses. For many potential medical imaging products, it simply would not be possible to administer the amount of drug required to achieve the test dose. Concentration of a product in order to administer the high doses of required could be problematic if altered physical chemistry changes the product's performance.

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The above comments on Group criteria are relevant, as well, to intravenously administered microbubbles, microaerosomes, and other related microparticles used in diagnostic contrast sonography. These drugs are biologically inactive and are administered in low mass doses in conjunction with an imaging examination. Like radiopharmaceuticals, gaseous ultrasound contrast agents are eliminated from the body rapidly and completely with little opportunity for accumulation to toxic levels. The frequency of administration of ultrasound agents is also limited to single dose or limited repeat doses. In spite of this, the proposed safety factor of 1,000 would eliminate these agents from Group 1 designation.

Nycomed Amersham requests that FDA reevaluate the criteria for Group 1 designation and suggests that a no-observed-adverse-effect-level of 5 times the maximal human dose for entry and retention in Class 1 is more appropriate.

Regarding the role of clinically blinded reads, Nycomed Amersham recognizes the importance of eliminating bias from efficacy evaluations. We are requesting, however, a reevaluation of the reader characteristics and blinding criteria proposed in the draft guidance.

Nycomed Amersham believes that the requirement that a reader not be affiliated with an institution where the study was conducted in inappropriate. Because of the difficulty sometimes encountered in finding readers with enough experience and expertise to evaluate new agents, particularly in large studies, we suggest that readers from the same institution as an investigator be allowed to participate if not involved in the study. Investigators should be permitted to read images that are obtained from study sites other than their own. This would improve and facilitate selection of the appropriate readers without introducing bias into the evaluation.

Fully blinded reads provide an assurance that bias is reduced in a purely statistical sense; however, they produce a highly inaccurate measure of the effectiveness of the drug as it will perform in the clinical setting. Data generated by fully blinded reads have limited utility to clinicians. Except for fully blinded reads standard imaging with clear anatomy, such as a chest x-ray, fully blinded reads are generally inappropriate.

A sequential unblinding model applied to contrast agents results in the generation of a significant number of data sets. This volume of data could introduce confusion into the review process, increase the cost of studies, cause reader fatigue and present problems for recruitment of competent readers.

For most contrast agents, efficacy evaluations should be based on semi-informed readings where readers are provided with some information. Readers should not be provided with the final diagnoses or other "truth measure," information on the imaging protocol, dose, and method of administration or inclusion/exclusion criteria.

The use of truth standards should be reevaluated as well. FDA should clearly define methods for determining and demonstrating that a truth standard is in line with accepted

clinical practice. The Draft Guidance states that when a medical imaging drug is being developed for an indication for which another drug or diagnostic method is approved, a direct, concurrent comparison to the approved drug or diagnostic method is encouraged. Sponsors are also encouraged to use the same truth standard. At the March 26, 1999, public meeting, an FDA representative stated that sponsors were not obligated to use a comparator product in addition to a truth standard. Nycomed Amersham requests that this be stated explicitly in the Draft Guidance.

Specific Comments

Page 9, paragraph 3: the statement "imaging with the contrast drug product should add value when compared to imaging without the contrast drug product' should be changed to "imaging with the contrast drug product under optimal parameter settings should add diagnostic utility when compared to imaging without the contrast drug product under optimal parameter settings."

Item B1 should reflect the 'accepted' gold standard when it exists.

Page 11, D.1.a: The term 'reliably locate' should be defined.

Page 12: In the definition of appropriate representation, does the adequate representation of the spectra of normality and abnormality imply the need to enroll in proportion to the incidence rates in the target population? This should be clarified. In the last paragraph, 'parameter's normal range" should be changed to a "parameter's range within normal subjects."

Page 14: Does the sentence "In most disease or pathology detection..." preclude broad indication? Current wording seems to suggest that it does.

Page 14, Section 4: "Appropriate patient management means that diagnostic or therapeutic management decision are validated as being proper based on the correct diagnosis of the patient or clinical outcomes." If the diagnostic or therapeutic management has to be based on the correct diagnosis (truth or clinical outcome) there is no choice either to compare to the truth or to evaluate the effects of the product on clinical outcomes, e.g. on diagnostic or therapeutic management, since the diagnostic or therapeutic management has to be based on the correct diagnosis.

Page 22: The guidance states that "[a]t lease two independent, blinded readers...are recommended for each study that is intended to demonstrate efficacy (p. 26) The guidance also states that goals of Phase 2 studies can include providing preliminary evidence of efficacy. The guidance should clearly state that this does not necessarily imply that at least two blind readers are necessary for phase 2 studies. "...confirm the principal hypotheses developed in earliest studies.." is not the goal of phase 3 studies. Common endpoints should be used across phases but the nature of the hypotheses differs.

Page 26: Regarding the number of independent readers, in the case that the endpoint results in the reduction of interobserver variability, it would be more appropriate to read a part of the patient data by several readers rather than to read all data by two or three readers. Otherwise it would not be possible to prove reduction of interovserver variability in a reliable way. Two or three readers cannot represent reader variability.

"Randomization of images refers to merging the images obtained in the study (to the fullest degree that is practical) and when presenting images in this merged set to the readers in a random sequence." The guidance should clearly state that randomization of images are to be done only after all images that will be presented to the blinded readers have been obtained, if this is what the FDA intends.

Page 29, C.2: For contrast drug products, the results of the unenhanced images should generally not be incorporated in the truth standards. The unenhanced image may be the truth for the primary efficacy endpoint, or the best standard available.

Page 31: If the use of a placebo is primarily for safety, the guidance should state that images obtained with the use of placebo should still be evaluated for efficacy.

Nycomed Amersham requests that a discussion of statistical power considerations in the Study Analysis section be included.

Nycomed Amersham appreciates the opportunity to provide comments to the draft guidance document. Because of the critical issues outlined in these comments, Nycomed Amersham requests that the Agency consider the above comments and issue a new draft guidance for public comment prior to adopting the final guidance.

Respectfully Submitted,

Susan K. Olinger
Director, Drug Regulatory Affairs
Nycomed Amersham

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